(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 879 823 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
22.01.2003 Bulletin 2003/04

(51) Int Cl.[7]: **C07H 17/08**

(21) Application number: **98303945.4**

(22) Date of filing: **19.05.1998**

(54) **Preparation of azithromycin**

Herstellung von Azithromycin

Préparation de l'azithromycine

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **19.05.1997 PT 10200697**

(43) Date of publication of application:
25.11.1998 Bulletin 1998/48

(73) Proprietor: **HOVIONE INTER LTD.**
6000 Lucerne 7 (CH)

(72) Inventors:
- **Heggie, William, Dr.**
  Cabanas, 2950 Palmela (PT)
- **de Mouro Vaz Azevedo Mendes, Zita Maria**
  1000 Lisboa (PT)

(74) Representative: **Wain, Christopher Paul et al**
A.A. Thornton & Co.
235 High Holborn
London WC1V 7LE (GB)

(56) References cited:
WO-A-94/26758
US-A- 4 517 359

EP 0 879 823 B1

Printed by Jouve, 75001 PARIS (FR)

Description

[0001] This invention relates to the preparation of azithromycin.

[0002] Azithromycin is a well-known semi-synthetic macrolide antibiotic (U.S. patent nos. 4,474,768 and 4,517,359). It is prepared through the expansion/inclusion of a nitrogen atom in the macrolide ring of erythromycin A, followed by reductive methylation. Azithromycin is more stable and more effective, particularly against gram-negative bacteria, than erythromycin A.

[0003] The reaction sequence to transform erythromycin A into azithromycin involves extremely strong and aggressive reaction conditions (J. Chem. Soc. Perkin Trans. I, 1881 (1986)), and requires the isolation of intermediates which, in certain conditions, are even more unstable than the starting material. Reaction conditions and isolation procedures must be mild and very strictly controlled. This can give problems when a laboratory scale process is put into practice on an industrial scale. Additional restrictions have to be included in the manufacturing process in order to ensure that the azithromycin is obtained in good yield and high purity.

[0004] The transformation of erythromycin A into azithromycin involves conversion of erythromycin into its oxime; Beckmann rearrangement of the oxime to the imino ether of erythromycin A; reduction of the imino ether to 9-deoxo-9a-aza-9a-homoerythromycin; and, finally, reductive N-methylation to obtain the azithromycin.

[0005] The reduction of the imino ether step and the reductive methylation step have so far been described in a two stage process (EP-A-0109253). This enables separation and purification of the intermediate 9-deoxo-9a-aza-9a-homoerythromycin before proceeding to the second stage. However, we have now appreciated that having a two stage process of this sort is undesirable and we have found that, surprisingly, it is not necessary and that significant advantages can be achieved by using a different procedure.

[0006] According to the present invention, it has been found that an imino ether of erythromycin can be reduced, and the product thus obtained can be subsequently submitted to reductive methylation in the presence of the same noble metal catalyst and in the presence of formaldehyde or a source thereof, without any isolation of the intermediate product. The two reactions already known *per se* can thus be conducted using the same catalytic system in the same reaction vessel and in the same reaction medium. By carefully choosing the reaction conditions, one can obtain a product of good purity and with a good yield. Thus, the present process represents a considerable industrial advantage over the prior art by reducing the number of reactors and manipulations, like the isolation of the intermediate product.

[0007] The invention thus provides a process for the preparation of azithromycin from an imino ether, which process comprises reduction and reductive methylation of said imino ether carried out sequentially with a noble metal catalyst and hydrogen in the presence of formaldehyde, or a source thereof, and wherein both reactions are conducted in the same reaction vessel.

[0008] According to published literature, the conditions which have been found to be most effective for the reduction of the imino ether involve utilisation of reducing agents in stoichiometric amounts or high pressure hydrogenation using platinum (WO-A-94/26758). This is then followed by isolation of the cyclic amine, which is then subject to reductive methylation employing the well-known Eschweiler-Clarke conditions (formaldehyde and formic acid in chloroform) or by hydrogenation (formaldehyde and hydrogen in the presence of a noble metal catalyst) (U.S. patent no 4,517,359, J. Chem. Res., 1988, 1239-1261).

[0009] Reduction of the imino ether using sodium borohydride (EP-A-0109253, J. Chem Soc. Perkin Trans., I, 1986, 1881) involves an extremely exacting procedure as far as completion of the reaction and recovery of the product are concerned. The initial intermediate present in the reaction medium is apparently a boron containing complex, which must be destroyed in order that the desired 9-deoxo-9-a-aza-9a-homoerythromycin can be isolated. The complex in question must be eliminated under acid conditions and since, as is known, the macrolide is sensitive to acid media, the conditions for this step must be rigorously controlled. This procedure becomes even more difficult on an industrial scale, since the times of contact between the sensitive intermediate and the undesired aqueous acid medium are inevitably more prolonged.

[0010] In the present invention, these difficulties are reduced or completely overcome by synthesising the 9-deoxo-9a-aza-9a-homoerythromycin intermediate, preferably under mild conditions, so that it is not necessary for it to be isolated or purified prior to the following step. Naturally isolation of this intermediate can be effected, if so desired. The reduction is generally carried out at a temperature between 0-50°C, the preferred range being between 20-25°C. At these temperatures, side reactions such as hydrolysis of the glycosides present in the molecule are reduced, especially hydrolysis involving the cladinose unit.

[0011] The process of the invention can be conducted in any suitable organic solvent. The preferred solvent is acetic acid, containing different percentages of water. Other organic solvents, such as ethanol, tetrahydrofuran, dioxane or mixtures thereof with water, can also be used.

[0012] Pressures which lead to the best results and to acceptable reaction times are those between 20-70 bar, but other pressures outside these limits can also be used.

[0013] The preferred reduction catalyst is 5% rhodium-on-carbon, although other noble metal catalysts, such as platinum, palladium or ruthenium, can also be used. The amount of rhodium used can vary but we prefer to use from 0.5 to 2% calculated with respect to the

starting material. The use of amounts outside this range can result in changes in reaction times which can be a disadvantage.

[0014] The formaldehyde is preferably provided as a 37% aqueous solution thereof or as para-formaldehyde, although other sources can be used. The amount of formaldehyde used is generally from 23 to 100 moles/mole of the imino ether. A further smaller amount of catalyst may be added so as to complete the reaction within a reasonable time.

[0015] If desired, the catalyst can be recycled and reused several times, thus rendering the process more economic.

[0016] The azithromycin is isolated by adjusting the pH of the reaction mixture to between 9 and 10. In this manner, it is possible to obtain azithromycin of acceptable purity. Crystallization from a mixture of ethanol/water can yield a product with a sufficiently high purity for it to be used as starting material in the pharmaceutical industry.

[0017] The present invention affords, among others, the following advantages: namely two chemical reactions in only one reaction vessel; use of less sophisticated industrial equipment, given the fact that one of the intermediates is not isolated; and the use of milder reaction conditions, giving a pure product with a high yield.

[0018] The following non-limiting Examples illustrate the present invention.

EXAMPLE 1

[0019] To a solution of 2 g (2.7 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 20 ml of acetic acid, there was added 0.03 g (0.38 mmoles) of sodium acetate and 0.5 g of wet 5% Rh/C (11.25 mg Rh). The mixture was then hydrogenated at a pressure of 70 bar and at 40°C for 3 hours. At the end of this period, 27 ml of an aqueous solution containing 37% formaldehyde (0.36 moles) was added under atmospheric pressure and at room temperature, and the mixture hydrogenated at 40 bar and at a temperature of 40°C for 20 hours. The catalyst was filtered off and the filtrate evaporated until an oil was obtained. To the oil so obtained, 45 ml of water was added, and the pH of the solution was adjusted to 9.3 with NaOH 4N. After stirring for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 1.2 g of crude azithromycin with a purity of 97% after recrystallization.

EXAMPLE 2

[0020] To a solution of 4 g (5.4 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 20 ml of acetic acid, there was added 1 g of wet 5% Rh/C (22.5 mg Rh). The mixture was hydrogenated at 60 bar and at a temperature of 40°C for 5 hours. At the end of this period, 22.5 ml of an aqueous solution containing 37% formaldehyde (0.3 moles) was added under atmospheric pressure and at room temperature, and the mixture was then hydrogenated at 40 bar and at a temperature of 40°C for 20 hours. The catalyst was filtered off and the filtrate evaporated until an oil was obtained. To this oil, 90 ml of water was added, and the pH of the solution was adjusted to 9.4 with NaOH 4N. After stirring for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 2 g of crude azithromycin with a purity of 97% after recrystallization.

EXAMPLE 3

[0021] To a solution of 8 g (10.9 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 32 ml of acetic acid and 8 ml of water, there was added 8 g of wet 5% Rh/C (180 mg Rh). The mixture was then hydrogenated at 70 bar and at room temperature for 2 hours. At the end of this period, 40 ml of an aqueous solution containing 37% formaldehyde (0.54 moles) was added, and the mixture was hydrogenated at 40 bar and at a temperature of 40-45°C for 20 hours. The catalyst was filtered off, and the pH of the filtrate was adjusted to 9.4 with NaOH 4N. After stirring for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 7 g of crude azithromycin with a purity of 95% after recrystallization.

EXAMPLE 4

[0022] To a solution of 4 g (5.4 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 4 ml of acetic acid and 16 ml of water, there was added 4 g of wet 5% Rh/C (90 mg Rh). The mixture was hydrogenated at 70 bar and room temperature for 2 hours. At the end of this period, 25 ml of an aqueous solution containing 37% formaldehyde (0.34 moles) was added under atmospheric pressure at room temperature and the mixture was hydrogenated at 40 bar and at a temperature of 40-45°C for 24 hours. The catalyst was filtered off, and the pH of the filtrate adjusted to 9.4 with NaOH 4N. After stirring for 2 hours at room temperature, the precipitate was filtered off, washed with water, and dried, yielding 2.8 g of crude azithromycin with a purity of 98% after recrystallization.

EXAMPLE 5

[0023] To a solution of 8 g (10.9 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 24 ml of acetic acid there was added 8 g of wet 5% Rh/C (180 mg Rh). The mixture was hydrogenated at 70 bar and at room temperature for 2 hours. At the end of this period, 50 ml of an aqueous solution containing 37% formaldehyde (0.67 moles) was added under atmospheric pressure at room temperature, and the mixture was hydrogenated at 40 bar and 40-45°C for 24

hours. The catalyst was filtered off, and the pH of the filtrate was adjusted to 9.5 with NaOH 4N. After stirring for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 6.1 g of crude azithromycin with a purity of 98% after recrystallization.

EXAMPLE 6

[0024] To a solution of 4 g (5.4 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 18 ml of acetic acid and 2 ml of water, there was added 2 g of wet 5% Rh/C (45 mg Rh). The mixture was then hydrogenated at 70 bar and at room temperature for 2 hours. At the end of this period, 35 ml of an aqueous solution containing 37% formaldehyde (0.47 moles) was added under atmospheric pressure at room temperature, and the pH was adjusted to from 3 to 4 with NaOH 4N. The mixture was hydrogenated at 40 bar and at a temperature of 40-45 °C for 24 hours. The catalyst was filtered off, and the pH of the filtrate was adjusted to 9.4 with NaOH 4N. After stirring for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 2.7 g of crude azithromycin with a purity of 96% after recrystallization.

EXAMPLE 7

[0025] To a solution of 8 g (10.9 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 8 ml of acetic acid and 32 ml of water, there was added 8 g of wet 5% Rh/C (180 mg Rh). The mixture was hydrogenated at 70 bar and at 40°C for 2 hours. At the end of this period, 10 g (0.33 moles) of para-formaldehyde was added under atmospheric pressure at room temperature, and the pH of the reaction mixture was adjusted to 4 with NaOH. Hydrogenation was carried out at a pressure of 40 bar and at a temperature of 40-45 °C for 24 hours. The catalyst was filtered off, and the pH of the reaction mixture was adjusted to 9.2 with NaOH 4N. After stirring for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 4.98 g of crude azithromycin with a purity of 97% after recrystallization.

Claims

1. A process for the preparation of azithromycin from the imino ether of erythromycin A, which process comprises reduction and reductive methylation reactions of said imino ether with a noble metal catalyst and hydrogen in the presence of formaldehyde, or a source thereof, and wherein the reactions are conducted sequentially in the same reaction vessel.

2. A process according to claim 1, wherein the formaldehyde or a source thereof is added at the beginning of the reduction.

3. A process according to claim 1, wherein the formaldehyde or a source thereof is added at the beginning of the reductive methylation.

4. A process according to claim 1, 2 or 3, wherein the noble metal is Pd, Pt, Rh or Ru.

5. A process according to claim 1, 2, 3 or 4, wherein the formaldehyde is provided as formalin or as paraformaldehyde.

6. A process according to any of claims 1 to 5, which is conducted in the presence of acetic acid or formic acid or another organic solvent.

7. A process according to claim 6, which is conducted in the presence of ethanol as organic solvent.

8. A process according to any of claims 1 to 7, wherein the acidity is controlled by use of a buffer.

9. A process according to claim 8, wherein the buffer is sodium acetate.

Patentansprüche

1. Verfahren für die Zubereitung von Azithromycin aus dem Iminoether von Erythromycin A, welches Verfahren Folgendes umfasst: Reduktions- und reduktive Methylierungsreaktionen des Iminoethers mit einem Edelmetallkatalysator und Wasserstoff in Gegenwart von Formaldehyd oder einer Quelle desselben, wobei die Reaktionen sequenziell im gleichen Reaktionsgefäß durchgeführt werden.

2. Verfahren nach Anspruch 1, wobei das Formaldehyd oder eine Quelle desselben zu Beginn der Reduktion zugesetzt wird.

3. Verfahren nach Anspruch 1,wobei das Formaldehyd oder eine Quelle desselben zu Beginn der reduktiven Methylierung zugegeben wird.

4. Verfahren nach Anspruch 1, 2 oder 3, wobei das Edelmetall aus Pd, Pt, Rh oder Ru besteht.

5. Verfahren nach Anspruch 1, 2, 3 oder 4, wobei das Formaldehyd als Formalin oder als Paraformaldehyd bereitgestellt wird.

6. Verfahren nach einem der Ansprüche 1 bis 5, das in Gegenwart von Essigsäure oder Ameisensäure oder einem anderen organischen Lösungsmittel durchgeführt wird.

7. Verfahren nach Anspruch 6, das in Gegenwart von Ethanol als organischem Lösungsmittel durchge-

führt wird.

8. Verfahren nach einem der Ansprüche 1 bis 7, wobei die Azidität durch Anwendung eines Puffers unter Kontrolle gehalten wird.

9. Verfahren nach Anspruch 8, wobei der Puffer aus Natriumacetat besteht.

Revendications

1. Procédé pour la préparation d'azithromycine à partir de l'imino-éther d'érythromycine A, **caractérisé en ce que** ce procédé comprend les réactions de réduction et de méthylation réductive dudit imino-éther par un catalyseur de métal noble et d'hydrogène en présence de formaldéhyde ou d'un dérivé du même, et où les réactions sont réalisées de façon séquentielle dans le même réacteur.

2. Procédé suivant la revendication 1, **caractérisé en ce qu'**on ajoute, au début de la réduction, le formaldéhyde ou un dérivé.

3. Procédé suivant la revendication 1, **caractérisé en ce qu'**on ajoute, au début de la méthylation réductive, le formaldéhyde ou un dérivé.

4. Procédé suivant les revendications 1, 2 ou 3, **caractérisé en ce que** le métal noble est le palladium, le platine, le rhodium ou le ruthénium.

5. Procédé suivant les revendications 1, 2, 3 ou 4, **caractérisé en ce que** le formaldéhyde est foumi sous la forme de formol ou de para-formaldéhyde.

6. Procédé suivant l'une quelconque des revendications 1 à 5, **caractérisé en ce qu'**il est réalisé en présence d'acide acétique ou d'acide formique ou d'un autre solvant organique.

7. Procédé suivant la revendication 6, **caractérisé en ce qu'**il est réalisé en présence d'éthanol comme solvant organique.

8. Procédé suivant l'une quelconque des revendications 1 à 7, **caractérisé en ce que** l'acidité est contrôlée en utilisant un tampon.

9. Procédé suivant la revendication 8, **caractérisé en ce que** le tampon est l'acétate de sodium.